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that also lack biological markers.

If so, how do you deal with them? Can we learn something from your criteria for efficacy in dealing with drugs for those diseases that might help us in thinking about Alzheimer's?

DR. KATZ: I think, if I can start to answer that for the Agency, there are a couple of distinctions I want to make. First of all, my understanding of the trial design issues for other psychiatric illnesses, those, generally speaking, tend to all be well-controlled, usually placebo-controlled, trials.

The issue of how one measures outcomes in those diseases, as compared to Alzheimer's, is one that might crop up in later discussions and later panels in this symposium. I think we are going to spend a lot of time on how does one assess outcomes in patients with Alzheimer's disease. I don't know that they are, necessarily, directly analagous to how one does it in other psychiatric conditions.

DR. WURTMAN: I think it would be helpful if, when we have those discussions, we can have some insights as to how you do it for other behavioral diseases that lack lead drugs and biological markers.

DR. KATZ: I agree. I think the lack of biological markers, to hone in on that particular point, isn't necessarily a major problem. Also, just to back up for a second,

there are other effective drugs in other conditions.

DR. THAL: I would just like to comment on the issue of biological markers. It is true there is no biological marker for Alzheimer's disease, but as I will demonstrate to you in one slide, we are not bad in making the diagnosis. If you were to, now, look at the pathological series that have been published in the last seven years, the diagnostic accuracy rate based on a clinical examination and a neuropsychological evaluation averages sensitivity and specificity of about 85 percent.

If one uses NIN, CDS, ADRDA diagnosis of probably Alzheimer's disease, diagnostic accuracy is about 92 percent compared to pathology. So we certainly can pick out the populations who had Alzheimer's disease and nothing but Alzheimer's disease for our clinical drug trials, and these trials will be contaminated by about an 8 percent incorrect diagnostic rate.

I think that is actually pretty good.

DR. WURTMAN: The question, though, Leon, is can you pick out a 15 percent improvement in a patient with diagnosed Alzheimer's disease.

DR. THAL: You can pick out an improvement of any magnitude, given you are willing to study enough patients. I will show you some extrapolations and figures of actually how many patients you need. It simply depends on the sensitivity

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of your test instrument and its standard deviation.

I will give you an example. We are not dealing with stroke studies, but I attended a meeting on stroke methodology a few months ago. Most of our Alzheimer's trials deal, often, with about 200 to 300 patients. I thought that was a large number until I attended a meeting dealing with stroke.

Stroke is a much more variable disease. First of all, it occurs acutely and some patients get better in a matter of a few minutes or hours because they have had TIA's and not strokes. That is a very large contamination if you want to do an acute stroke intervention.

The recovery rate from stroke is highly variable. Some people become completely normal, and some are left with a fixed neurologic deficit. To deal with these statistical issues, current stroke trials that are being carried out in the United States and Europe are now employing upwards of 2000 to 3000 patients in order to design trials that can produce answers because of the variation in the patient population.

We are not dealing with anything near that issue. The course of Alzheimer's disease, although highly variable, when placed in perspective to stroke, is relatively predictable.

DR. KATZ: Let me also say one thing about the lack

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of biological markers. I don't believe that we consider it, from the regulatory point of view, necessarily an impediment to the development of drugs. There are many conditions for which there are no biological markers, and the law allows us, or perhaps obliges us, to focus on clinical phenomenon.

There are the problems, as you enumerated them, with how does one measure the relative clinical phenomenon. Nonetheless, specifically with regard to biological markers, I don't know that that is really a problem for us.

DR. DAVIS: I just want to take us in a slightly different direction and elaborate on some of the questions that Peter raised in his initial conversation. I think few would have any doubt that double-blind controlled trials are the standard of the field, the only way to establish efficacy. The real question, however, for this field is the one that Peter raised, and that has to do with heterogeneity.

If we have a condition that affects 2 million plus people in the U.S. and in equal number in Western Europe, and we have a treatment that might only affect 20 percent of them, that is still a very substantial number of people that can have a real public health impact.

The question becomes, what kind of design can we use that might reliably identifiy that subgroup and show that, in fact, they are responding. It's a very difficult problem.

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It has been approached in some methodological treatises by multiple crossover designs to show that people are repeatedly responding. It has been approached in studies that are going on in our field by some a priori stratification and identification, or enrichment.

I think these are the tough issues that we have to face, and I am sure there won't be any consensus. But it is certainly a conundrum for the field at this point.

DR. WHITEHOUSE: I think this heterogeneity issue is key, too, Ken. I think, as you suggested, there are some pre-hoc things that you can do like stratification. The issue of rechallange, I think, is something that is talked about a lot but not done. So, if you do identify 20 percent of your group that responded, then the next thing to do is take them off and then put them back on, and see if the same 20 percent reponds, or see if it is a different 20 percent.

DR. DAVIS: And that would seem reasonable except for the problem that in a degenerative disease, it is conceivable that responsivity will change over the course of the illness which makes it, again, equally complex.

There are no simple solutions, but clearly, rechallenge is something that we could do a lot more of and it relates back to, I think, David's initial point which is that if we move immediately from animal studies to double-blind, parallel-controlled, investigations, we make a big

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mistake.

We make the mistake of being able to identify, early on, some hint of whether the drug is doing something preliminary to ever thinking about NDA application, clearly. But I think companies might save themselves a lot of money by getting some reflections at a few good centers of whether an agent in which there is unlikely to be false positive response has any responsivity at all.

DR. FERRIS: To follow up on that issue in terms of what, in recent years, has been a major gap between what is discovered preclinically, generally in rodent models, and then jumping right into full-scaled Phase III trials, there is an awful lot in between. It doesn't just involve, necessarily, small human trials.

A lot can be done at the preclinical level in terms of looking at just what the drug is doing in rodents, moving to primates, and, furthermore, in early human trials, at least trying to look at similar kinds of processes and functions in man that were apparently showing drug effects in animals.

I will have a little more to say about that later this afternoon.

DR. KATZ: To address something that Dr. Davis had mentioned, and others, the notion of starting out small, small pilot studies, perhaps uncontrolled studies, what is

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the likelihood, or what is the evidence, for that matter, that you will see something meaningful in such studies.

If you are not going to see anything large, and so far we haven't in large well-controlled trials, what is the value of starting off small, a few patients, where the results would be unreliable, at best or, for that matter, in which a promising treatment might be rejected because it just couldn't be picked up in a small trial.

DR. DRACHMAN: I would like to make a comment about that which is that you don't have any idea of the patient population that will respond. In the drug study that I alluded to that is underway, patients who have severe Alzheimer's disease are being eliminated right from the very beginning. As far as I know, it is the vegetative patient in the nursing home who would profit the most from this drug. I don't have any idea.

It isn't clear from rats that run a maze that you identify a Mini-Mental State of 13 to 23 as the ideal population to treat with a particular drug. It isn't clear, even from a population like that, that what you want is individuals under a certain age, over a certain age, with a certain degree of deficit, with a certain type of deficit, those with obstreperous behaviors, those who are behaving perfectly normally.

So if there is a drug which is psychoactive and

which has some -- I use that word with apologies, by the way, but which has some reasonable effectiveness, and you don't hvae any idea of the group of individuals who could benefit the most from it, you have to try to find out.

The second part of your question which is suppose it has a very tiny benefit, which is one of my favorite problems in this field; that is, suppose thousands of Alzheimer's patients could benefit by a single point on their IQ scale, using the WAIS, would that be of value as compared with a few hundred patients who could improve their IQ's by 20 points. That is, the precise level at which you set your threshold for success will determine whether or not a drug can, in fact, be tested other than with a very rigorous trial in order to get an idea of who seems to be benefitting from it so you can then zero in and do the double-blind study with parallel structure later.

But you need clues, I think.

DR. THAL: I want to make one point coming back to the issue of subgroups. That is always somewhat of a disturbing issue because the issue of subgroups makes the assumption that there is something biologically different about the disease in different patients.

I think that is perfectly viable if you can actually show a biological difference. However, I caution people that, to my point of thinking -- and I am going to

take an extreme point of view for point of argument's sake. This is like saying that a person that has polio involving his left foot is different than a person that has polio involving his right arm.

They look different but they are both caused by the same disease, and I don't think that I would look for two different types of treatment for these two individuals with polio.

To my mind, at this particular point, Alzheimer's disease does appear to be a unitary disease process. I am taking an extreme point of view. You are all entitled, and will undoubtedly disagree with me. But until somebody is able to convincingly demonstrate, from a biological point of view, that there are multiple etiologies of Alzheimer's disease or that the biology is clearly different, I think we should be very careful about biological subgroups.

Secondly, while I think it is perfectly reasonable to look for subgroups for treatment, one also has to remember that once a drug is marketed and labeled for treatment of Alzheimer's disease, it is going to be used by essentially all patients with Alzheimer's disease.

You may think that is a good idea or a bad idea, but that is what is going to happen. And I think that is worth some discussion as well.

DR. WURTMAN: I think the problem with Alzheimer's

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is not multiple etiology, the problem is finding one etiology for starters. I think that analogy to polio, unfortunately, isn't very good. At this point, ten years into it, I think we know less about the etiology of Alzheimer's than we thought we knew five or six years ago.

One is reminded of the situation with cancer thirty years ago when there were people who said it was caused by viruses, and people who said it was caused by toxins, and people who said it was caused by genes, and people who said it was caused by waves. Of course, they were all right, weren't they, as it turned out, in retrospect.

I think that with Alzheimer's disease, one can make the strong case that dementia does not, necessarily, equal Alzheimer's disease in all patients, that Alzheimer's is not necessarily one disease, that the underlying biologic theories we have had that Alzheimer's is related to the death of neurons may not be correct.

Certainly, at this point, as my colleague next to me, I'm sure, will agree, one could say the loss of choline acetyltransferase can no longer be taken as evidence of the death of the neurons that had contained it. We can no longer say that the plaques and tangles that Dr. Alzheimer saw are necessarily related to the pathogenesis of the disease.

In fact, it has been suggested that they may reflect just the opposite, namely, an attempt on the part of

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neurons to grow faster.

So I think, at this point, we really know next to nothing about the etiology, whether it be 1, 2 or 6 of Alzheimer's disease and the likelihood of it being heterogeneous, I would say, is far better than it being a homogeneous entity.

So there are two rather polar views.

DR. REISBERG: I would like to response to some of David's comments regarding finding drugs that work, and also some of Ken's comments regarding methodology.

It seems to me that we are, today, at a point of tremendous potential opportunity in terms of Alzheimer's research. I am thinking back to what Paul said, the dictum "rarely to cure, sometimes to treat, always to comfort." It seems very clear, from my standpoint today, that there are many symptoms in Alzheimer's disease, and David was alluding to some of these symptoms, which are, clearly, likely to be amenable to pharmacologic intervention.

I am speaking of symptoms such as agitation and verbal outbursts and violence and axieties and obsessive behaviors. And it seems very clear to me regarding the reserach on Alzheimer's that many of these potentially remediable symptoms are, clearly, a major source of burden for caregivers of the Alzheimer's victim. They seem to be a cause of premature institutionalization.

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They also seem to be a cause of increased morbitidy in the Alzheimer's victim.

The methodology exists today. This is a very, very important part, I believe, of the meeting here today, to separate out these probably potentially remediable behavioral symptoms, sometimes to treat, from other symptoms, cognitive symptoms, which may not, today, be amenable to pharmacologic intervention.

Clearly, there is a need to treat the primary cognitive symptoms of the illness process. Indeed, this is the reason that many of us are here today.

However, there has been a tragic historic error made in Alzheimer's disease research and that is that the cognitive symptoms in the illness have been mixed with the behavioral symptoms in the illness. The result has been that treatments have been promulgated which have very, very subtle effects on behavior.

These subtle effects on behavior have translated into equally-subtle effects on cognition. Of course, these very subtle effects on cognition have been deemed to be of enornous significance.

There is some tendency -- and I think this is very important for us here today, in terms of our methodologic discussions -- there is some tendency today, also, to mix these symptoms together. It seems to me that if we continue

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to do this, we will have a plethora of treatments which truly do nothing to relieve the burden of the caregiver, nothing to relieve the illness in the patient.

These ineffective treatments will draw resources, enormous resources, from the search for truly effective behavioral interventions and truly effective cognitive interventions. And we will, eventually, proceed to methodologic discussions, but I will simply say that there is methodology today for separating the cognitive and the behavioral symptoms.

Some of David's comments regarding the range of patients relates to this. At a certain range, early in the disease, you can get patients and exclude patients who have any behavioral disturbances, and look at cognition very, very carefully using many different measures, and show whether or not a drug does anything cognitively.

At the other end of the spectrum, as David was alluding to, there are other patients who are very, very agitated. We need to study the agitation in those patients and see what the effects of any medications are in cognition.

It seems to me that the hope and promise of this meeting is that it will bring us closer to the very modest solution that Paul invoked; sometimes to treat.

But I also think there is a danger in this meeting today. There are methodologies which are extant, which will

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bring us further away from the solution and we may end up with a plethora of treatments which really do nothing.

DR. KATZ: I think that the methodology to study the specific symptomology is something that we will get into. I want to bring back the discussion a little bit towards the original focus, the need for clinical trials, controlled trials, and to combine it with something that is gaining some credence here, the notion of the small pilot trial in the development of a trial.

How does that jibe with what Dr. Whitehouse was talking about, which I believe is a very real phenomenon; that is the public's perception of the role of clinical trials, the necessity to have drugs available right away with a glimmer of hope? How does the small, possibly encouraging, pilot trial -- what does that do to the formal, definitive clinical trial in the public's mind and in the mind of the community?

DR. WHITEHOUSE: To answer that question, I think the public doesn't have a sense of when there is a small trial and when there is a large trial. That is the whole problem, not understanding the whole process of development. That is the responsibility of people who publicize small trials as if they are definitive trials.

I would, again, like to stay within the heart of what I think the focus of this session is, and focus on the

natural history control because the law allows that kind of a control group as included in the same category as providing efficacy.

I don't consider that in the same category. I consider a natural history control as more akin to these kinds of small -- it doesn't have to be small in terms of number -- but, at least, lower rank in terms of being able to convince me of efficacy.

But I wonder if we can get some consensus on that from this group as to whether natural history controls are in the same standard of providing evidence for efficacy, but also wondering whether, as we learn more in Marshal's center and Ken's center and David's about the natural history, whether on a site-specific basis, natural history controls can, in fact, become a second-rank but more effectively-used way of screening medications.

I don't consider them in the same rank, even though they are in the legislation. But I wonder if there is more of a role once we understand the natural history a bit more, at least at specific sites recognizing that the heterogeneity across sites is quite great, whether that is something that should be explored further.

DR. KHACHATURIAN: I would like to put a slightly different spin on the discussion and identify the problem slightly differently; that is, I think it is similar to the

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points that Peter alluded to. The issue, as I see it, is trying to find a balance between two conflicting needs.

One is the regulatory need to determine safety and efficacy, which is the law, through controlled trials. I think that speaks for itself. I think there is a need for it. I don't think that should really be challanged. Perhaps we can improve the process. The other is the need of the patients. There is something like 4 million people affected by this disorder in one way or another, and there is a need for immediately dealing with that problem.

I am wondering whether there is a possibility to examine whether those two needs, conflicting needs, could be met, that is to carry on the controlled clinical studies as has been done in the past with other drugs. I don't think that should change, but, at the same time, to find a way where the needs of the patients are so desperate could be met.

After all the public that is really raising questions about the clinical trials is coming from that pressure, that the patient has some problem now, they are not being included in the trial, they see the need for immediate relief.

DR. KATZ: I have my own thoughts on that, as I'm sure you know. I would like to open that particular question to the panel.

DR. KHACHATURIAN: I was going to suggest some

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solutions. At the present time, we have the means to do both, I think, because we have the centers, a large number of other programs supported by NIMH and other groups where we have access to patients. Perhaps when a new agent becomes available, when a trial is being proposed, a first screening could be done of all the eligible patients that are going to be likely to be included, that meet the criteria for the trial.

Once that has been done, there should be a second segment of patients that are not likely to be included in the trial that still could benefit from the trial. Perhaps these could be put in the --

DR. KATZ: Excuse me; benefit from the drug or benefit from the trial?

DR. KHACHATURIAN: Presumed drug that in the minds of the clinicians perhaps could benefit. A parallel study that is less controlled could go on, but without really interfering with the results of the clinical trial.

If this kind of an approach, perhaps, could address the needs of the FDA and the scientific community as well as the community out there that is really desperately for some resolution.

DR. KATZ: This is a real problem, and it has been proposed in other contexts besides Alzheimer's disease. As I say, I have my own strong feelings on it, but I would be

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interested to know what the panel thinks about that.

DR. FERRIS: I think this really is a problem, and I have some serious concerns about whether there really is a feasible way to do this that would not ultimately overwhelm the process we are most interested in.

Peter spoke briefly about the issue of placebo response in Alzheimer's studies. He mentioned one very critical aspect of that placebo response, and that is the placebo response of the patient's family. I think anyone who has done studies with Alzheimer's patients, whether they have documented this phenomenon or not, have seen it over and over and over again.

The patient will suddenly remember something. It might be the only thing they have remembered in years, and that is suddenly taken as a dramatic improvement by a family member. It actually can infect the professionals doing the trial. It is a potential contaminant of one sort or another leading to, perhaps, a placebo response on the part of the investigators.

My fear is that to the extent that there would be, in parallel with the kind of trials we all want to see, less desirable experience with the drug in terms of scientific rigor. There would be, I think, potentially be so much feedback of information from those trials, particularly into the media, for example, that it could really destroy the real

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scientific investigation of a compound.

And I really see this whole issue of the attack on the process we all seem to agree is essential, namely placebo controlled trials, as a very serious one. It reminds me somewhat of the Animal Rights movement and so forth which is, perhaps, coming out of a different context but, nevertheless, when there is an upsurge of public response of one sort or another, I think that the people that know better, the people here in this room, including the industry people, need to properly respond.

I am just seconding what Peter said in his opening remarks. I think it is very important for all of us, in a concerted way, to defend the slide that Peter showed.

DR. FOLSTEIN: I would just like to briefly support Zaven's position but with a slight spin of my own on it. First of all, I think that there is absolutely no question that clinical trials more than other scientific endeavors are a social process as well as a logical process, and that the social process of clinical trials in Alzheimer's disease is very critical.

One of the functions of critical trials is to maintain hope. We have been talking about giving false promises, but in fact a physician's responsibility is to maintain hope. Really having a trial maintains hope and is good for the patients, and it generates a lot of other

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research.

So I would be in support of finding some way of having more controlled clinical trials. I would probably not want to have them be less stringent, but one example that I could think of would be to find a way of permitting trials of safe substances in Alzheimer's disease. I think Hydergine is a perfect example of it, not to bring up all the baggage that goes with Hydergine, but you could logically think of lots of kinds of compounds that would be safe.

For example, antioxidants or aspirin; you could think of a pharmacological rationale for using them even though you don't expect the possible payoff to be very high.

But the initiation of such trials, in and of themselves would be productive of hope in the patients and would relieve some of this pressure that everyone feels that operates these centers. I mean, on every visit, the patient says, "Well, is there a new drug yet?"

And we say, "Well, no. We are just following you longitudinally." That's not very helpful to them.

So we really do need more trials. But I think that we don't want to lower our standards as far as the controls are concerned, but rather we should increase the possibility of using more safe substances.

DR. DRACHMAN: I would like to follow up on what Zaven said and second it and, perhaps, put a little other

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emphasis on it. Clearly, we are trying to deal with the science of determining the validity of a drug for the treatment of Alzheimer's disease here. But it is equally clear that that isn't what we are doing at all.

What we are really doing is fending off the supposed and real attacks from the media, demands from the public, the -- shall I use the negative term -- avarice of those who might even profit from some things as drugs have worked in this sphere so that, at the same time that we are trying to make a scientific decision about precisely how we can determine the success of drugs, we are really dealing with a whole lot of other problems simultaneously.

I frequently visualize -- Paul, I haven't told you this -- but I frequently visualize Paul as Horatius at the Bridge. I'm sure some of you remember that scene, Lars Porsena of Clusium, "By the nine gods he swore," and it is clear that such an event is always hovering in the background.

How we deal with trials is influenced both positively and negatively by our perception of how the public, the media, the drug companies, the individual investigators who want their names in lights, even for fifteen seconds on Twenty-Twenty, or whatever it is. All of these things are really influencing how we respond.

I think we should take them apart. I think we should deal with them one at a time. How do you determine

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the effectiveness of a drug is one. How do we deal with the legal requirements it two. How do we keep the media off our backs is three. How do we work with a type of drug industry which, as I have frequently told people, has profits that make the crack industry look trivial at times, is four.

So, frankly, I think we do need to separate these. I am often in the center of this, as many of you are well aware. Every time something like this comes out in the press, or threatens to, my phone rings -- until October, anyway when I no longer am in the role where I have to respond to every such claim.

But I do believe that we have to separate these when we deal with how a drug works. Does it work? Can you test it this way? What do you release to the press? What becomes an official accepted drug? Separate issues.

DR. WURTMAN: The problem you articulated very well. The FDA seems to have a dual responsibility; one is a certification responsibility. I sense universal agreement that there should be no dilution of the scientific criteria that the FDA uses to certify drugs. The second is basically almost a political-administrative-economic-social responsibility acting on that certification and determining what is what is not allowed to go public.

Perhaps what we need is a separation of these responsibilities in which is either some second body assists

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in allowing for exceptions or a new category of drug allowance develops in which a drug, based on inadequate certification, could be made available, let's say, for a year or two and then, after massive use during that time, a reassessment based on clinical grounds could determine whether making that drug available has been politically, socially, and maybe even scientifically, useful.

DR. KATZ: I want to say that there are mechanisms -- the whole regulatory mechanism for the development and regulation of drugs is fairly flexible. There is a specific mechanism known as the treatment IND which allows a wider exposure to a drug which has not yet met the regulatory requirements for approval, but about which we know a great deal, including the fact that it works.

There is strong evidence from control trials that it works and that it is reasonably safe. So I don't know that there needs to be a special mechanism that allows -- but again, it allows it late in the process and there are defensible reasons for that.

DR. DAVIS: We, sadly, have to deal with the media. The political reality is Alzheimer's disease affects many people. Now, it is not necessarily a bad thing that our constituency wants to be informed because that constituency are the very people who make possible the funding for the kinds of breakthroughs that then go ahead and stimulate drug

development.

If we are dealing with cholinergic drugs, it is because there was funding that demonstrated what the neurochemical defects are and when, in the next decade, we deal with drugs that may change the processing of the amyloid precursor protein, that will be directly related to the extraordinary increase in funding that we have seen for Alzheimer's disease that, in fact, is a result of mobilizing constituencies who have an interest, appropriately, in finding a treatment.

The question for us becomes this: we need them. They deserve the information. How can we perform our role and still inform them.

I think we can't run away from them, but we just have to stand up for what we believe is the necessity for rigorous science. But I don't think it is appropriate to believe that when Twenty-Twenty calls, or when the phone rings off the hook, that we can run away from them.

DR. RASKIND: Do I have to be as entertaining as the other panelists, or should I just do my own thing. I just want to address the topic. Our group at the University of Washington just published a very small placebo-controlled trial of an antidepressant drug in patients with Alzheimer's disease who met criteria for depression.

To our shock and surprise, the antidepressant

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worked very nicely and the placebo worked equally as well. This is in a non-cognitive type of symptom, the type that Barry has referred to. But it was surprising to me how many people were upset at this finding because everybody was sure that in their practice, when they treated unhappy or depressed Alzheimer's patients with tricyclics, these drugs were effective.

In fact, I was actually mad at myself, because I had the same feeling. I am now totally convinced that no matter what aspect of Alzheimer's disease you wish to treat, a controlled trial is absolutely necessary. Furthermore, if you base your judgment of efficacy on large clinical experience after several years, all of these drugs will be effective.

Everybody believes, especially if they have a convincing care provider, that whatever is being given to them is working somehow, at least the care providers do. And I think that is dangerous.

Final point; these trials which I think are very important for the Alzheimer centers and for the community of Alzheimer care providers and victims are also extremely expensive, not only financially expensive but expensive in the time which investigators who, perhaps, could be discovering something important about the processing of the amyloid precursor protein, in case that turns out to be

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important, are, in fact, performing these clinical trials.

I think there is going to be a point at which the morale issue is going to be somewhat self-defeating. If these trials are not producing, over time, and a lot of effort goes into them, both the investigators and the Alzheimer's victims and caregivers who are participating are going to start questioning what we are doing.

I am not giving any answers, but I think that trying everything in huge trials is something to be avoided.

DR. KATZ: I would ask the speakers to speak close and directly into the microphones.

DR. REISBERG: Of course, as Peter underlined repeatedly, controlled trials are necessary in medical research, generally, but also -- and this is really an extension of the point that you were just making, Murray, there are various reasons why controlled trials are particularly necessary in Alzheimer's disease research.

One of these reasons is the horizon phenomenon; that is, that in Alzheimer's disease today, we are literally at the horizon. There have been no treatments which -- and I think any of us will stand up and say they believe -- have been convincingly been shown to be effective in alleviating either the primary cognitive symptoms of Alzheimer's disease, and even as we both know very well from our reviews of this literature, even the other symptoms of Alzheimer's disease,

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the behavioral symptoms.

These statements apply both over the short term and over the long term, and also prophylactically. This horizon phenomenon places us at a point of tremendous opportunity because if we get anywhere with anything on any symptom, then we are a little bit off that horizon.

However, this horizon phenomenon also presents us, and I think we have all experienced this, with an enormous, enormous pitfall; that is, that any deviations off the horizon, if they are real, immediately assume enormous significance. And we can only distinguish, for the various reasons that have been alluded to here, because of effects on family members was translated into effects on clinicians and, indeed, may translate into effects on patients, as well, the care that they give the patients.

We can only distinguish these very important issues with very, very carefully structured controlled trials.

DR. THAL: I would just like to refocus on Peter's question. I think everyone has agreed that to definitively release a drug, one needs a controlled trial. What about the issue of what do we do with those patients that are not in clinical trials, but who want access to the drug? To what extent should the drug be made available to them outside of clinical trials, and how should that be done?

DR. DAVIS: I will try that, Leon. Most people

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who come to centers don't enter trials because of exclusion criteria. Most people, in our experience, who then come to the center and even enter trials ultimately are disappointed. So we have a large cadre of people who are either not getting drugs because they have other system disease and can't get them, or get drugs and then when the trial is over, except for an occasional member, say, "So what?"

Disappointment is what is our stock and trade. I see very little that we can do about that unless we have agents that are so safe we can distribute them to everybody. However, the question of the treatment IND is very important and, perhaps, sometime in the next two days, we should spend some time discussion when is there enough promise that a drug can be extended to a treatment IND and it can be broadened to include individuals who otherwise may not be available to trials.

DR. WHITEHOUSE: What I do if somebody is not eligible for a study is, in fact, set up a mini kind of study for them with either Hydergine or lecithin with an idea that they would, at least, be participating in a process of looking at something that in both those case is safe.

I think there is a great danger in creating other studies that would be time consuming and expensive to study drugs that we are really only interested in giving to people to assuage their need to be in a big study.

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Again, I go back to my main focus that we need to educate people about how the process occurs. So much of the desire to be in studies is, I think, based on misinformation. And it is based on, also, a degree of selfishness. It is kind of like a question that I was asked yesterday; it is the ultimate question for a doctor. "If it was your mother who had the disease, which study would you have her in?"

And I said, "I would feel not obligated to have her in any," but I would like to have her in something so that she could participate in the process that as a society we are going through trying to develop an effective medication.

So rather than try to have people be motivated to get in these studies on misinformation and kind of a selfish need to get the latest thing, let's try to educate them about the process and about how they can participate. Even if they are in the placebo group, they are still making a contribution and they are still fighting this illness.

I really thing that long-term -- and it is long-term -- that having people understand what we are doing a little bit better is ultimately the key. I also object to some of the comments that I have heard here that are negative towards the media. Just as we have to educate the media, we have to learn from the media and learn what their needs and desires are, as well, because we can, more effectively, work together.

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To create an adversarial situation is not a good idea.

DR. THAL: I would like to return back to the original question before we run out of time; that is the need for clinical controlled trials. Every one of you has come up with the position that you agree that we do need controlled clinical trials. We haven't, I don't think, fully discussed the control issue.

We have had some discussion of placebo controlled trials. We have had some discussion of historical controls. Can I get a little bit more discussion on the types of control groups that are appropriate for these trials? The question is, does anyone feel that anything other than a placebo controlled group is appropriate, so that we can at least reach some closure on the issue, if possible.

DR. RASKIND: I would be happy to start and maybe finish. I'm a sorter when it comes to Alzheimer's disease as far as course of illness. The more patients you see, the more you are impressed that the progression of the disease is not homogeneous, at least in the period of two, three or four years, or two years, say, we are talking about. So I think historical trials are very dangerous in this area.

I don't think they can be interpreted.

DR. KATZ: Are there no subpopulations of patients with the disease, either in terms of their symptomatology

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and/or their severity of their illness for whom the natural history is so well-defined that they could possibly be amenable to study in an historical control?

DR. DRACHMAN: That isn't quite true, of course. But I think that deals with a ridicula ad absurdum. If there were a patient who was in a nursing home and non-verbal, who, given a drug, woke up and spoke in an intelligent fashion, I don't think we would need a great many placebo controls to recognize that this is somewhat beyond the ordinary effectiveness of lecithin, shall we say.

So part of the argument involved here has to do with the order of magnitude of the effect that one is attempting to discover as to whether or not you truly need placebo controls. We are talking, as was so nicely put, about the horizon effect. I would agree that if we are looking for barely-detectable improvements in minutiae of behavior, we certainly do need placebo controls.

In fact, every drug that we have been able to study so far, we clearly need placebo controls. But should there be a different kind of drug, I think we could consider the alternative of historical or experiential controls.

DR. FERRIS: This raises another issue, of course, or another distinction that needs to be made. I think if you start thinking about the possibility of natural history type of control situations, you are really beginning to need

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to separate what the target of treatment is; namely, the distinction between improving symptoms during a relatively short period of days or weeks or a few months versus possibly, down the road, putative treatments that show the course of further progression, further deterioration, of the patient.

I think in what we are all basically doing now, namely attempting to reverse symptoms in the relatively short term, the placebo control is going to be indispensable because there isn't really much to look at in terms of distinctions and in change in symptoms or downward course of symptoms over relatively short periods.

On the other hand, if we were talking about a study, which virtually hasn't been done, to look at the effect of a compound over two, three, four, five years, where we have a pretty good idea what kinds of changes would occur, at least on a group basis, over a three, four, five year period in 100 Alzheimer's patients who were properly diagnosed.

I think, then, there are opportunities to not necessarily have to be as rigorous in terms of placebo control.

DR. KATZ: Which brings me to a question I want to raise. We don't have much time, and it may be discussed in the next session, but what do people feel is the appropriate duration for a trial in Alzheimer's disease? From a regulatory point of view, if a bona fide drug effect could be

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shown in a very brief period of time, that would meet the letter of the law, but what would the pane think, again briefly, about what is an appropriate duration of time?

DR. DAVIS: I had early on, based on some of the studies that we had done, that effects could be shown very quickly. I have come to change that view. The reason I have is twofold. The first, when one considers some of the animal models, for example, in the Pass Avoidance Task, a very short-acting drug is given at ~~one~~ point and a behavioral effect is noted 72 hours later.

In people dealing with issues like memory, it may be that the brain can function marginally better for some time before there are obvious behavioral changes of what are a marginal increment in the neurobiology.

That has been borne out to me by my clinical observations which my bias was that it would be a short time, but my clinical observations are, now, that some of the larger effects happen towards 6 weeks. So I don't know how long it could be. It might be longer than we have ever been doing.

DR. WURTMAN: There is a corollary question. This is, should the duration of treatment be long enough so that the placebo group will show a deterioration, and how many months does it take before one gets a statistically-significant deterioration in the placebo group? And, if they

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don't get a deterioration, or if most of them don't, perhaps did they really have Alzheimer's disease.

DR. THAL: I will answer that question in the next session with some data. What I would like to do is open it for questions or comments from that audience.

DR. LEBER: I want to raise an issue very rapidly with you because I think everyone agrees that control trials, at least on this panel, are necessary for the confirmatory, regulatory decision. But you are leaving the audience with, perhaps, the perception that it is not unreasonable to use small, open trials that rely upon clinical judgment to determine whether or not a new drug is an appropriate lead.

I think that that is something that you all recommend, but I would like to ask you what evidence you had that that really works. I understand that serendipity in the prepared mind has been a very appealing thing, and that clinicians like to promote what some statistician once called the myth of clinical judgment.

Just look at the strategy. You are dealing with a situation in which you are arguing that the low prevalence of a trait which allowed someone to respond to a drug is what you are seeking to find.

If you were dealing with this in a situation where you had two urns, one with ten black marbles out of a thousand, the other with two black marbles out of a thousand,

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and your job was to find which urn had more black marbles, would you sample five at a time, ten at a time, or five-hundred at a time?

That is almost the thrust of what I am getting at. Even though this is appealing on the surface, it may, in fact, be self-defeating to suggest that small samples, because of sampling error, sampling strategies, and the low prevalence will detect anything other than, perhaps, satisfy your fancy.

DR. WHITEHOUSE: When Collisions found penicillin, there were no controlled studies. They didn't need them. So it depends, Paul. It depends on a lot of factors. If you think that you have got something that is really very good, you can do it in one patient.

(Inaudible question from the audience.)

DR. THAL: That is a controlled trial that you are describing. You are simply describing a crossover controlled trial. There certainly have been lots of crossover controlled trials done in dementia for a number of drugs, yet they have not demonstrated efficacy.

So that is an acceptable form of a controlled trial. It has drawbacks, but it is an acceptable form.

DR. KATZ: Lets take one more question. It would be useful if you could come to a microphone and ask your question into the microphone so all the people could hear it

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and it could be recorded.

MR. GREG HILLMAN: I am Greg Hillman, the Ernest Hillard Foundation. I was wondering of the panel could address the question of at what point do you think it is unethical to continue randomizing patients in any trial?

DR. THAL: Is the question randomization or is the question continuing treatment, or withholding treatment from the placebo-controlled group?

MR. HILLMAN: The question is withholding treatment from the placebo control group; at what point do you think you have enough improvement in the group receiving the drug that you consider it to be unethical?

DR. KATZ: Let me say that stopping rules, so-called, for clinical trials are more or less well-established and there are different ones. Those are, in fact, contingencies that are often built into protocols. I don't think you can say, a priori, what is enough, or how much of an effect in how many patients. It needs to be worked out.

I think it is time for the session to end. I want to thank all our panelists. I think we have reached at least a consensus that for definitive efficacy requirements, placebo-controlled trials are required.

The discussion was, indeed, far reaching. It would be useful if everyone could be back here for the next session at exactly 11 o'clock.

[A break was taken from 10:50 to 11 o'clock.]

SESSION II: GUARANTEEING EXTERNAL AND INTERNAL VALIDITY

DR. LEBER: Welcome back. This is the start of Session II which has the interesting title of External and Internal Validity. The one thing I like about validity is that there are so many of them.

There are validities that deal with the content of areas of information. There are concurrent validities which basically mean that people can agree on things. There are construct validities which mean we think we know what we are talking about. There are many private idiosyncratic definitions of validity, so I have to explain what the intent of this particular panel and session actually is.

We are making the assumption that I was prescient enough to figure out what the vote would be during the session, and I think I was, that most experienced clinicians and investigators and neuroscientists recognize that, at least for the definitive answer on whether or not a drug is effective, one has to rely on the controlled clinical trial.

Controlled clinical trials are simply a nominalism. You can't describe them unless you describe them in detail. Obviously, a controlled clinical trial is more than something listed in the compiled Federal Register, 21 CFR314.126. It is not just five types of controlled clinical trials that the Agency would accept.

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It involves everything from the nature of the patient sample that we are going to intend to recruit to be representative of the illness that we wish to extrapolate the results of our experiment to, issues that were brought up, for example, by Dr. Drachman earlier; shall we narrowly focus on a particular range of the Folstein, Folstein and McHugh Mental Status exam? Should we pick on people who are already in pelvic curl and see whether we have a drug with a Lazarus effect?

Should we be looking at people who are early in the predictive stage, if you will, or possible stage of dementia and may not have it and we will have to wait for time to pass to determine retrospectively whether, in fact, they are demented? So: issues of sample which are critical to issues of validity, probably more to external than internal validity, but that, in itself, is an arguable point.

What about the question of design issues? How is it that you do a study which is really based on an age-old -- I mean, I am not going to be upstaged with historical references no matter how eloquent and entertaining the are. You know, this whole idea of doing controlled trials is really from John Stuart Mill. There are various ways to prove things. There are methods of agreement which don't work to well because there are a lot of jokes about that, and I won't get into them.

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There is the method of difference which is really the method we all rely upon. One applies two interventions. One sees with result with and without the intervention, and if there is a difference between them, we conclude we have a drug effect, or whatever other effect we are looking for.

In a sense, that is what all clinical trial methodology of the type we are talking about is really dealing with. But, what way to do it? When we talk about prospective, randomized controlled ~~cl~~inical trials, what are the details. In addition, what kind of interval are we going to be observing? Under what conditions? Should they be in patients who are already hospitalized, which has not happened very often, by the way, to Alzheimer's patients because of the game in which I could describe third-party payers handle the problem?

Shall we deal with nursing-home patients? Shall we deal with ambulatory patients who are afraid that they may, in fact, be Alzheimer's? Those kinds of questions always emerge?

How long? This was a question that Dr. Katz tried to bring up in the last session and there wasn't enough time. It is not simply the pharmacodynamic/pharmacokinetic problem of how long this drug will hang around. It is conceivable as Dr. Davis was pointing out that the plasticity of the nervous system lags well behind the administration of the

drug.

For all we know, it is a light switch that, once thrown, takes a long time to produce or light up, as somebody used in a recent meeting I went to, the image of turning on the light switch in a gym. You know those lights that take a long time to get to maximum brightness. The application of the treatment? There is a dwell time and then the full flower of the response is seen.

If you don't study it long enough in that sense, you may have missed it.

But that is not all. Somebody was pointing out earlier, you can't step in the same river twice. Therefore, we have questions of just how long a clinical trial ought to go to capture something meaningful. An effect that lasts two days that does disappear, as Dr. Davis suggested, might be, in effect, not worth looking at. Maybe it is only a first treatment effect and doesn't persist beyond the first week.

It is an arguable proposition that one would want to approve a drug of that sort because what benefit will accrue if you continually treat someone with a drug that works only for three days and then never works again? So issues of how long and how to prove how long the drug works are important and not from a strictly regulatory point of view, but from a sensible, public-health dollar compassionate

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reason as well.

What happens to the drug has some risk. It is has been our experience -- not just mine, but certainly collectively, that there are darned few drugs in the armamentarium that are very powerful that aren't, in some way, dangerous to somebody.

The example of using aspirin was mentioned earlier, but I am struck by the fact that people who do NSAID studies are always aware that a certain percentage of the patients, I think over 1 percent, probably have a GI bleed and many more may have non-detectible GI bleeds.

So the drugs that we attribute innocence to, that we are so familiar with, may, in fact, on a public-health scale be quite dangerous. Once again, there is the issue of risk and benefit; how long, for how much, and is that doable?

We have all sorts of other questions which, obviously, have to be addressed. When we get through doing a particular study, we may, in fact, have an internally-valid result; that is, using the method of John Stuart Mill, we have compared, contra rotula, and we find a difference internally. We conclude that in this particular experiment, the drug is effective, but to whom is the result extrapolated? Just how far can we go?

Are we going to talk about all demented, pre-demented, Alzheimer's insipio, or whatever we want to call

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it, people afraid they may have it, and so on? In our societies, you know, once the drug is on the market, the physician is left to his decision or her decision to decide just what other individuals can be exposed to it.

So we bear a responsibility in approving any drug for how it will also be used even though it is not the Agency's responsibility. I would argue it is the responsibility of the academic and medical, and actually, the whole society, to discern what we are doing when we do it. We ought to consider things beyond labeling.

At least in terms of the moral and ethical judgment, at least I hope that people external to the Agency will give us their thoughts about.

That is sort of our hope for this session. Clearly adequate and well-controlled trials, or adequate and well-controlled trials in the sense they allow valid conclusions -- that word again -- that can be extrapolated to labeling claims that will allow sponsors to market their products profitably and successfully, but truthfully.

Let me now turn to the opening presentation on this issue. We are lucky enough to have as a Chair of our Advisory Committee an individual who is an expert, literally, in the field of drug development in dementia. Although we have not seen a proven success in his area, I am sure he believes that he is well on the way to having successes that

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will serve as the first robust example of how to do it and how to do it right.

Once that is there, I think our task will be easier. At any rate, Dr. Thal, in addition to working in cholinomimetic therapies is a neurologist. He has been involved with the Agency over a long period of time before he was on our Advisory Committee, perhaps in a more adversarial way, arguing about the conditions of his actual use of clinical trials.

But it has been a delight through the decade that I have known him and dealt with him to be able to listen to what he has had to say and learn from him. And so today, I am delighted to have him come forward and offer his comments on external and internal validity.

Dr. Thal.

DR. THAL: Thank you.

[Slide.]

I am only going to touch upon a couple of the points and items that I am actually scheduled to discuss with you, but I also want to deal with some of the issues that we are not dealing with currently; that will have to do with some of the design considerations for future drug trials which include some understanding of our knowledge about the rate of change in this disease, and to present you with some early observations and some information that may prove to be

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useful for you.

The definition that we all use of dementia is very straightforward and simple. This is really the DSM-3 definition. We are all familiar with it and it is really nothing new to any of us.

When we start out looking at a population to carry out a given drug trial, this is the kind of initial definition that we will use in order to come up with a population suitable for study. And we are defining dementia as a deterioration in intellectual functioning which impairs cognitive or social performance.

Obviously, we are interested in the core symptom which is memory.

[Slide.]

We have further honed down our diagnostic criteria so that for most of the clinical drug trials that are currently underway, we are interested in patients with Alzheimer's disease. The groups of Alzheimer's patients that are available to study have really been categorized further into three groups; those individuals who have definite Alzheimer's disease, meaning biopsy proven, who we have essentially none of for our studies.

We have a second group of patients who meet the NIN, CDS, ADRDA criteria for probably Alzheimer's disease. These are really a relatively clean group of patients and in

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most of the Alzheimer's centers make up about 70 percent of the patients that we see. These are individuals that have a clear-cut deficit in two or more areas of cognition, who have an insidious onset of disease and progression, normal level of consciousness.

If two neurologists, or a neurologist and a psychiatrist saw the patient, in general, we can all agree on the diagnosis. Indeed, in our own center, several individuals review the charts on these patients, and the degree of consensus is really quite remarkable. We think we have a pretty good handle on this diagnosis, and on a relatively pure group.

[Slide.]

We then end up with another group of patients whom we often end up diagnosing as having possible Alzheimer's disease. These are individuals who, indeed, look like that have Alzheimer's disease but something else is going on.

For example, this is the patient who presents with a visual agnosia as the first presentation of their disease, turns out to have a memory deficit. We think that the patient has Alzheimer's disease, but we are not certain. Or there is the patient who has a concomitant medical condition such as a thyroid disease or some other medical illness that may produce dementia, but in the clinician's point of view is not responsible for the dementing illness.

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The question is, what should we do with this group of patients; should they be included in our drug study? Should they not be included in the drug studies? If we don't include them, what happens when we have carried out a drug study on a group of patients who met the diagnosis of probable Alzheimer's disease. The drug is now released. Is it suitable to extrapolate from our very, very pure sample population to a less pure population to a less-pure population and apply the drug, and expect to see the same kind of therapeutic effect.

This is a question I am not going to answer for you, but one that I think we should come back to in discussions at the panel. So diagnostic criteria are one consideration.

[Slide.]

The second consideration, really, has to do with the issue of how severe a patient should we include in our trial and what should the range be. One could span the spectrum and say, "Well, I'm only going to include patients who score between 20 and 23 on the Mini-Mental State," or, "I'm going to take all Alzheimer's patients regardless of stage of disease because this is the group that I ultimately intend to treat with the drug."

In reality, we end up doing neither of these, and we end up compromising on some very practical grounds. We

end up compromising on practical grounds because we design a drug and we need to test that drug. We need to use instruments, and all of the instruments that we deal with have some degree of flaw or ceiling effect, so that if we use a Selective Reminding Task, that is an inappropriate task to use in a nursing home patient population.

On the other hand, for a highly-functioning lawyer who is having some mild memory problems, it is probably insufficient to look at a simply behavioral rating scale and say this individual has or has not been improved.

And so we tend to pick patients that we can examine with the clinical scales that we have available to us. This captures a particular slice of the population and, once again, if a drug is marketed, we then are going to expand the use of the drug from the narrow slice of population to patients with varying stages unless, of course, the regulatory agency says that one has proven the drug to be effective only in a certain stage of disease and cannot be used for individuals who do not fall within that stage.

Of course, that will never meet the test of clinical practice, since as Dr. Leber pointed out, it is up to the clinician to make the decision about what condition to use a drug for once that drug has been marketed.

So I think that becomes a very important issue, and I think our initial approach to dealing with it is that, yes,

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initially we wish to use as pure a population as possible for two reasons; one, we wish to answer the question as to whether or not the treatment will effect and change Alzheimer's disease alone uncomplicated by other conditions and that once that is proven, we need to expand the scope of the clinical trial and include other patients that have other concomitant diseases in order to determine whether or not the drug will still have efficacy in a more complicated state.

And similar statements can be made for the degree of disease; that is, we pick a fairly narrow group that we can test and later on, if the drug is going to be used across the board, we need to expand the scope and range of the dementing population that we chose to treat.

[Slide.]

Dr. Wurtman raised the issue about how accurate our diagnosis is without the holy grail of a glucose tolerance test or a biological marker. I would like to return to that issue because there are now about seven or eight neuropathological series that have been published showing a relatively good accuracy in making the diagnosis of Alzheimer's disease. This is a series which I simply picked because it has a reasonable number of patients who reached autopsy.

These are 65 patients at the Western Ontario site published by Hachinski and Wade. 39 of these individuals met the clinical criteria for the diagnosis of either

possible or probable Alzheimer's disease and, indeed, at autopsy, 33 actually turned out to have Alzheimer's disease and nothing but Alzheimer's disease.

If you compute sensitivity and specificity, it is about 85 percent sensitive and about 85 percent specific. You say, "Well, what happens if you break it down by probable and possible?"

It turns out if you break it down by those categories and you use probable Alzheimer's disease, the diagnostic accuracy is about 92 to 93 percent. For just possible, the diagnostic accuracy drops to about 78 percent, but overall about 85 percent. I think that is pretty good. That is not bad.

That means that even if we include both probable and possible Alzheimer's disease patients in our clinical trials, we will have a misdiagnosis rate of only about 15 percent. I think that is, certainly, acceptable.

One may then ask the question, "Well, these are being done at university medical centers where patients are intensively evaluated. What is going to happen when the same kinds of criteria are applied by clinicians in the community?" This was actually answered in a study that was published within the last year in which a large series of brains collected by practitioners in the Massachusetts area were sent to a group of investigators in Boston for patholog-

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ical confirmation.

It turned out that just the general practitioner practicing anyplace in the state of Massachusetts was also about 85 percent correct in making the diagnosis of Alzheimer's disease. So I think we are not going to be dealing with a huge degree of contamination, and we can, indeed, turn up with patient populations that are suitable for study.

[Slide.]

Peter Whitehouse talked about the issue of trial design. I only want to touch upon it for a moment. These are, clearly, the kinds of features that we are interested in in a good trial design; randomization, adequate blinding, sample size. And I would like to emphasize the issue of a few outcome variables.

I think there is a major problem with clinical trials that are put together and have a total of 10 or 15 or 20 outcome measures because when I read that trial, I really don't know quite what to do with it. By chance alone, if you have 20 outcome measures at the .05 level, one will one positive outcome. I think this is a major issue.

The last issue is the issue of a meaningful relationship between the test variable and the clinical outcome. If we measure a one-point change on a verbal learning task, does that mean anything in terms of the relationship between that change and the way a patient lives

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his life, or the natural history of the disease.

I think we must link the kinds of changes that we are looking at on these scores to what is actually going on either in terms of the way the patient lives his life, meaning in Activities of Daily Living Scales, or we must link it to the progression of the disease in order for this to be a meaningful outcome from the clinical point of view.

I will give you some information about how we can actually accomplish that task.

[Slide.]

We have heard some mention before about the use of crossover studies from an individual in the audience, and I think that crossover studies can be useful. But crossover studies suffer from the problem of a series of assumptions; and the most important assumptions are, really, the following two: No. 1, that there is no carryover effect across treatment periods.

By carryover effect, I don't only mean the fact that the drug has cleared from the body. There can be other medical carryover effects, or there can be psychological carryover effects. All of these are assumed to be absent if one uses a crossover study.

The second major assumption underlying a crossover study is that the treatment response is the same in both periods. If one is dealing with a rapidly progressive

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disease, this is clearly not the case. That will never happen.

If one is dealing with a very slowly progressive case, that assumption may be met. And one can argue about whether the treatment effect will be the same or not in both periods in patients with Alzheimer's disease. The main advantage of a crossover study is that it saves money and you recruit fewer patients.

But there is a very nice paper published by Brown in 1980 in an obscure journal to me called Biometrics which deals with the efficacy and the cost saving of carrying out crossover trials. It turns out that if you have much more than about a 15 percent contamination rate, then economic considerations dictate that it is better to do a double-blind parallel trial up front and not to bother with a crossover trial.

So, yes, a crossover trial can be effective. It can save money, but it will not necessarily do so unless the assumptions underlying it are met. The major assumption underlying a parallel study is that you have equal randomization and that patients enter the two groups in an equal fashion and that there are no underlying differences.

That, indeed, is the only underlying assumption in demonstrating the efficacy of a parallel design study, and the reason that most of us have chosen that type of a design.

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It simply makes fewer assumptions.

[Slide.]

Dr. Leber made mention of some other weird type of designs that have been used in the recent past. I would like to show you another type of design and throw it open for discussion and bring up some of the problems with this type of a design. This is the design that is being used in the current THA trial of which Ken Davis is the principal investigator and is here in the audience and on the panel.

In this particular design, we introduced a dose titration phase initially consisting of four doses, now two, in an attempt to find a specific dose to which patients would respond. Now, I happen to think, and other people involved in this design, happen to think that this is a necessary step in a cholinomimetic agent because there are numerous, both animal and human, studies indicating that cholinomimetic agents have a fairly narrow therapeutic window.

One probably needs to seek this out. The question is whether one needs to seek this out for a group as a whole; and one could define a single one or two doses to which all patients would respond, or whether one needs to seek out an individual dose for every single patient.

I think that is an unanswered question. We will have more information about that when this trial has been completed. Obviously, that type of design is not applicable

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to other drugs. There are many other compounds that will produce an effect that does not show that type of pharmacological response, and where a dose titration is not necessary where the more you give probably the better a response you will see until the response plateaus off and where there is no associated toxicity with that drug, or where the therapeutic window is so broad that it is not necessary to carry out any type of a dose titration phase, where this can be carried out on a sample before the trial is undertaken.

In this particular design, we then have chosen to discard patients that did not respond during the dose titration phase in an enrichment design. Is this a good idea or a bad idea? Well, we thought it was a good idea because it gives us an enriched population in which to carry out a double-blind parallel trial.

Ultimately, it may turn out that there are problems with this and, perhaps, titration is not sensitive enough, and we are discarding potential responders. In addition, there are other problems with this design such as the imposition of the placebo in the last period.

We, too, are making the assumptions in the dose-titration phase that there is no carryover and that a person who responds, for example, to 80 mg of this particular drug has washed out completely when tested in placebo during the

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last period. This may, indeed, be an unwarranted assumption. So I don't want people to look at this and say, "Well, this is the way all drugs should be tested."

This was a specific design for a specific clinical drug in a specific clinical trial. And I hope it will answer our questions, but there are certainly criticisms of this design and there may turn out to be a series of problems that this design has not met.

[Slide.]

I mentioned a small number of clinical outcome measures. In many of the trials that I am currently involved in, I have tried to minimize the number of measures. I do think that in any Alzheimer's trial, however, you need to have at least two measures. One is you need to say something about cognition in that patient on your favorite local scale, and that scale must have validity with respect to something about the disease process.

Secondly, you need to say something about what is happening to that patient in an overall global sense or in activities of daily living, and that the drug must show improvement in both areas. If you can't show cognitive improvement, and you can't show improvement in overall functioning, you don't have a drug to treat dementia.

On that point, I will be fairly emphatic.

[Slide.]

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I now would like to turn away from the issue of treatment of symptoms to talk about types of treatments that we are going to contemplate for the future; that is, all of the drugs that we are currently testing are really drugs designed to induce acute improvement in patients. But they are not designed to change the natural history of the disease.

They are not even designed to change the rate of decline. Before we can design drugs to look at the change in the rate of decline, we have to define the natural history. And I would like to spend the last few minutes on that issue.

[Slide.]

This is a series of data that Bob Katzman and I put together looking at rate of change in a simple test called the Blessed Information Memory Concentration Test that most of your are familiar with. You can ignore most of the numbers and I will bring you through it.

What we did was to simply administer the Blessed test to a large number of individuals at four different sites and in four different stages of dementia; a nursing home population who were fairly demented, a private-practice group who were only mildly demented, a group of individuals in the Bronx Aging study which is a prospective study of individuals who enter the study non-demented and are followed prospec-

tively for the development of dementia, and the Alzheimer Disease Research Center in San Diego.

What we found on this very simple instrument is that, roughly, patients declined by approximately four points per year on the Blessed Information Memory Concentration Test, although when we further divided this into cortiles on the test, there seemed to be some ceiling effect or some slowing for the most demented patients, probably a ceiling effect.

But the bottom line is that patients deteriorated by roughly four points per year on this test with a standard deviation of four points. So we have some measure of change.

[Slide.]

This type of analysis has also been carried out by Ken Davis and Richard Mohs on the Alzheimer Disease Assessment Scale, and we have similar measures on this scale so that we know something about the rate of decline for this particular instrument.

[Slide.]

What I also wanted to show you, however, is the wide variability. This is a subset of just one of those four groups of patients in which I have simply plotted the initial -- actually, I want to make a couple of more points about the previous slide.

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When we carried out a further analysis of these groups to state, "Well, what were the predictive factors predicting rate of change?" it turned out that the rate of change was independent of sex, age, age of onset, site, ethnicity, socioeconomic status, amount of underarm deodorant you used and virtually anything else that we were able to look at, and that it seemed to be a relatively biological constant.

Much against my own clinical judgment, it turned out that, for example, young patients whom I had always felt deteriorated more rapidly than old patients did not deteriorate more rapidly, that their rate of decline was identical. It was also unaffected by positive family history for Alzheimer's disease.

So the rate of decline on this particular instrument seemed to be essentially a biological event, unaffected by all of the other factors that we looked at.

What I do want to point out is that even though it is relatively constant for a group, there is a tremendous amount of variability within these patients.

This is a subset, one of the groups of patients, in which we simply plotted the initial Blessed score versus the rate of change in points per year. The only point I want to make is that there is a lot of variation. Here is an individual who starts off making about eight errors on the

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Blessed when he is first seen and progresses by one point per year.

Here is another patient who starts off with eight points per year, but progresses by twelve points per year. So this patient has creeping dementia. This one has galloping dementia. But I, in advance, cannot tell you who will be in which group.

Here is a patient who presents with about twenty points and progresses almost not at all. Had I treated this particular patient with my mother's chicken soup, I would be able to conclude that the rate of progression in this particular patient was extremely slow thanks to her excellent cooking.

That might be an incorrect conclusion.

[Slide.]

We have also, more recently, looked at a group of, in this particular instance, 92 probable Alzheimer's disease patients. And we have looked at three particular instruments; the Blessed Information Memory Concentration Test; the Dementia Rating Scale of Mattis, and the Mini-Mental State Examination.

In the past, we have demonstrated good correlations between the Mini-Mental State and the Blessed. Again, these correlations were redemonstrated in this cohort of 92 patients. The real question we wanted to ask, however, was,

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"How do these tests change and, if we know the rate of decline between Points 1 and 2, can we, during the one year of disease, predict the rate of decline in the following year?"

[Slide.]

We computed the rate of decline between the first year and the second year, and then said, "Does the rate of decline between Year 1 and Year 2 predict the rate of decline between Year 2 and Year 3?" And these are the r values. They are exceedingly disappointing, again indicating both the variability of the disease and the variation that we see in our own test instruments.

So we are going to be dealing with test instruments that have fairly large standard deviations compared to the natural course of the disease process. I think this point should be kept in mind.

[Slide.]

How big a group of patients do you need to see a drug effect? Well, it is really pretty easy to calculate and you can eyeball it. It really depends only on the ratio of the standard difference to your standard deviation so that if you have a drug that has a pretty good effect, that can alter a change on a scale by one standard deviation, your standard difference would be 1.

If we are going to look for a change on the

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Blessed, and you have a drug that can cause a four-point change on the Blessed and your standard deviation is 4, your standard difference is 1 and, by God, you can get by with about 30 patients per group, not a very big trial.

But if you are going to try and reach for very small differences like a quarter of a standard difference, you are going to end up somewhere out here and you are going to need several hundred patients per difference.

[Slide.]

Now, I would like to extrapolate that to a set of assumptions about a drug trial that someone in the audience might think about designing for the future, that we want to change the rate of decline in patients with Alzheimer's disease.

I will just give you two sets of numbers. These are simplistic numbers that I derived myself, and we now have a drug that we are going to try in a group of patients, in a double-blind parallel study. We will administer the drug to patients and placebo to the placebo group. And we are going to make some assumptions.

In this case, we are going to look at, say, the Blessed score. It doesn't really matter what test instrument we use. We are going to say that we know that on the average these patients declined by four points per year, that the standard deviation of that test is about 4. The alpha failed

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to appear. An alpha of .05, two-sided test, with an 80 percent power and one year of follow up; how many patients do we need in each group in order to show an effect?

Well, we have a great drug, we think, and it is going to show the rate of decline from four points per year to one point per year. By God, we only need 28 patients per group. We would like to look at a less potent drug, one that will decrease the rate of decline from 4 to 3, only a 25 percent decrease, and we are now up to 251 patients per group or a total of 502.

So now we have to sit back and say, "Well, what is the smallest change in the rate of decline that we think is of any value?" We are clinicians, not statisticians. How small an effect would you like to see, how small an effect in the rate of decline would be a clinically-significant change?

I won't answer the question. We will come back to it at the panel.

I think that is the end of the remarks that I would like to make and I think we will just reconvene the panel and try and answer some of the questions that I posed.

DR. LEBER: I would like to thank you for a very data-rich presentation. You nicely parsed out some of the things we are going to have to think about carefully before we plan anything. Let's get started on that.

I am going to come down a little bit to the end of

the table because I noticed sitting in the audience before that one of the risks of being on the end was we thought we would be able to look across and see people down the table. But there is the risk of missing those in the middle.

So if you actually looked at the number of points of discussion made, the people at the very apex of this curve were seriously underrepresentative until the very last minute. So I am going to try to watch for them.

Without further ado, I will invoke the Katz rule that the cochairs will only intervene if things seem to be lagging beyond our tolerance. That changes the rules slightly because you have adjustments for individuals.

Where are we? What is a valid trial today? Notice the enthusiasm. Is there a gold-standard study? Let's assume we want to approve a drug and get it out there for the treatment of dementia, unmodified, unqualified, and we want to market it tomorrow. We think we have for some good basic science reasons a candidate drug, and let's assume, for the moment, that we are past the stage we were worried about before.

We now have preliminary clinical evidence that it probably will be effective. Would someone like to talk maybe about how they would design the study? Was the tacrine study good enough? Should it be de rigueur? Elkan?

DR. GAMZU: One of the things I think we should

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answer is, in series, some of the questions that you had. We could talk about specific trials. But I would have to agree with Leon that the trials should dependent on the nature of the compound, and the knowledge basis that you have at any given point.

I think that to try to even come up with the ideal trial is probably an error. But one of the things that you mentioned, and it was one of the comments that I get asked, certainly, and I'm sure many of the members of the panel get asked, and that is why don't we just treat patients who are at the very early stage of the disease because they are the ones who are most likely to respond.

They have the most intact cells left, the least damage. They are more likely to function with some improved pharmacology. I think that is something that we should talk about. I, personally, used to think that that was not an unreasonable thing.

I would now concur with what Leon suggested, and that is that you should use as broad a population as possible and that from the sponsor's prospective, the labeling is going to be, presumably, Alzheimer's and I think that we would like it to be Alzheimer's and not just a narrow indication.

I think that we tend to take upon ourselves burdens that are unreal because we don't have a standard compound and

that if we looked in the areas of depression, epilepsy, and other areas, we know that the compounds that are out there are effective only in a small percentage of the population. We do not go looking for those patients with epilepsy who respond to sodium channel blockers or have certain other aspects of it, nor do we usually do that sort of sorting for patients with depression.

Given the results that Leon showed just now, and that is the rate of decline until the patients are really not testable, that we should, in fact, try to be as broad as possible within the constraints of not allowing concurrent illnesses and concurrent medications.

So I think that that is a theoretical reason, and I would just argue from a pragmatic perspective that the outcome measures that we do have that we all agree are general global outcome measures are designed to look at the spectrum of decline from non-demented to totally-demented patients, and that there is only a narrow portion of those either at the top or the bottom of whichever scale you are using and that if you choose patients who are highly functional, that the probability of showing a numeric improvement is low.

That is just a statistical, pragmatic perspective, but I think there are some theoretical things. And I think that is one of the questions that gets answered, and it is

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one of the things that is bandied around. It would be nice to hear what the experts think. Are we focusing incorrectly by taking in as many patients as possible as long as they are testable?

DR. LEBER: The one thing that I would like to try to do this time is let's try to stay on this particular theme for a while. The question, if I can recapture it in a different way, is there any kind of maneuver that will enrich the population, making the population sample more likely to respond in an experiment.

That is really what the question is about because, in a way, the cholinergic challenge was an enrichment design. You want to enhance the likelihood of getting a treatment effect. Now, if you know you have such a stratification variable, you can do it.

So the question before the Committee is do you know of anything that would allow you to reliably suggest that you can increase the efficiency of sampling for antidementia drug trials.

DR. FERRIS: In my view, the answer is that there is very little data on that issue in an objective sense. Even if we look at the THA trial, it is being assumed that there is an enrichment, but we don't really know. If fact, what occurred to me in looking at Leon's slide outlining the design is that, with the wisdom of hindsight, there could

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have been a very nice test of that by not dropping the people who didn't show best dose, and randomizing them to different best doses and seeing if there was any difference in outcome between those you would have dropped and those that you didn't, which would have been not that pertinent to the question of efficacy but certainly pertinent to the question of whether you really succeeded in your goal of enrichment.

I think that a lot of the difficulty in whether there is an appropriate enrichment strategy has a lot to do with how much of the more basic kinds of studies, both preclinically and clinically, are done prior to getting into a real large-scale trial.

I think one of the purposes of, say, early clinical trials, certainly done in controlled fashion, is to try and zero in a better way rather than having to analyze a huge amount of data later on whether there are particular subtypes, at least in this context in terms of severity of disease, the milder patients, the more severe patients, or the whole issue of the appropriateness of individual dose.

I think that kind of thing can be ironed out, perhaps expensively, but in a series of Phase II type trials.

That also relates to the issue of numbers of outcome measures. I don't think anyone would disagree with Leon's suggestion that in these large, multi-center trials, when you are hoping that that is the data base that is going

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to lead to an NDA application, that you want to plan in advance to minimize the number of outcome measures.

On the other hand, if you don't really know in advance what kinds of outcome measures are sensitive to the effects of a particular compound, it means that, at least in early trials, you need to cast a much wider net with respect to outcome measures and hope that by using a variety of, perhaps, measures that are more sensitive to small effects, some of these more global measures might not be as sensitive to small effect, that could help you design that later trial.

DR. LEBER: So your vote is really for not only a broad net on the population but a broad net on the observational outcome measure.

DR. FERRIS: At least in the early stages of the development. I wouldn't suggest that in the final, big, multicenter trial. I hope you would have information gathered before you design that final trial.

DR. LEBER: Before we go down that alley, one thing Leon said, which I think is very provocative. He said you can't have an antidementia drug unless it produces an effect on some cognitive vector; I will put it that way.

Does the Committee agree with that, because that has a lot to do with your screening policy? If you say it only has to be cognition or memory, you don't need as wide a net. Does everyone agree that that is the sine qua non of

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an antidementia drug, or is that arbitrary, capricious and absolutely unsupportable?

DR. MOHS: I agree, by and large, because the fact is that those are the defining features of what dementia is, in the absence of impairments in those areas, you don't have a dementing condition. The one possible exception, I think -- and this came up in the earlier panel -- is it is conceivable that there are agents that are available, maybe even currently, that would be of some use in the medical management of cases of Alzheimer's disease that don't treat the primary symptoms of the disease but, nevertheless, are useful adjunct to treatment.

However, to have a real treatment that is specific for dementia, what defines dementia and makes it different from other neuropsychiatric illnesses is the cognitive impairment. So if you had a drug that was specific for dementia, it would seem that it would almost have to treat and produce some improvement in memory and cognition.

DR. LEBER: Let me play devil's advocate with you and ask you a question. Let's assume for the moment that there is a real -- and this is prejudging something that will come up later -- effective syndrome unique to dementia and it doesn't respond to classic antidepressants.

But let's say it responds because it is free frontal-lobe pathology to some increase in dopaminergic tone,

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L-dopa. You might be able to document that the reason that you get an antidepressant response is conditioned by the presence of dementia. Isn't that a legitimate antidementia drug effect?

DR. WHITEHOUSE: I think so. I think it is quite possible that the biological basis of some of the very disturbing and important clinical behavioral manifestations, non-cognitive manifestations, are dementia-specific in some sense and it would be unfortunate to assume that we are really merely treating other things that are the same in cognitively-intact people, anxiety disorders and depression, in the same way.

So I agree with you. I think it is dangerous to make that assumption.

DR. LEBER: I didn't say anything, you know. I was just raising a question.

DR. CROOK: I would say that would not be sufficient. Given all the problems with pseudospecificity, I think it may be a drug that is effective for treating depression in dementia, or some other secondary symptom, but it would seem to me that Leon is right that if it is truly to be an antidementia drug, it has to have some effect on memory.

My problem, I guess, with Leon's slide had to do with the clinical, global improvement. If, in fact, you must have a change in clinical, global improvement, then you

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could argue that it is not worth testing at all.

I think I have problems with that in several respects; one, going back to Peter's point which I don't think was fully resolved, about the active placebo. I wonder whether some of the trials that are underway now and some that, no doubt, will be undertaken are, in fact, blind and whether, where the measure is an assessment by the clinician, by the family, whether that can be affected by perceived drug side effects, or whether it is truly a blind rating.

Secondly, those are, generally, very insensitive ratings. Are you going to require that, or if a drug has an effect on an objective measure of cognition, of memory or some other important variable, is that enough in the absence of a clinical, global improvement measure given that you can measure, particularly in the earlier patients, cognitive variables in a much finer way, in much smaller gradations, that you can on a five-point or seven-point rating scale from perfect to absolutely impaired.

DR. THAL: I would like to respond to that. When I used clinical, global impression, I am not referring only to the clinical, global impression of change. I should really expand that to say that it has to be a clinically-observable effect by someone and that if you increase the point score of a dementia patient on any cognitive test that

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you show, but that neither a clinician nor a family member nor another member of society can discern that effect on that individual, then it is not worth releasing that drug.

I think the marketplace will prove that to be correct, that no one will use such an agent.

DR. RASKIN: I have no problem with that, but I would like to get back to the issue of power that you were showing on the screen. The critical element there, I think, is the sensitivity of the instrument -- at least that is one of the critical elements.

In that regard, I do feel, also, that cognition and memory are sort of the hallmark of dementia as thought disturbance is the hallmark of schizophrenia in some way. It has been demonstrated, particularly in the early stages of dementia, and particularly if you advertise in The New York Times for subjects, that you really have to push the limits of your scale to show deficit and to show change.

In that regard, I think if I am going to be measuring cognition and memory, I would try to get something like what Tom is doing, more than a rating-scale kind of measures; in other words, something that has inherent sort of face validity, one of the issues you are raising, some of those kinds of things. "Do you remember when you go out to shop what you forgot and where you left your keys?" that kind of thing.

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I am wondering if you use that kind of instrument whether you would need the kind of power that you had outlined in terms of the sensitivity issue.

DR. THAL: I don't know the answer. I think it remains to be demonstrated to develop such instruments. I will just give you sort of a synopsis. We sort of broadly looked at four instruments, now; namely the Blessed Information Memory Concentrations Test, the Mini-Mental State, the ADAS and the Mattis Dementia Rating Scale.

What I can tell you is that roughly the change that you see in a patient over a course of one year, on the average, equals the standard deviation of that test. That is about where we are at.

Now, you can devise better tests that have smaller standard deviations, I would assume, and it will make it easier to show an effect. But that is what we are dealing with, that is the data that we have in hand.

DR. LEBER: Are you measuring the standard deviation of the test or the standard deviation of the population to whom the test is applied?

DR. THAL: The standard deviation of the population to whom the test is applied.

DR. LEBER: So until we know how to select the population and make it less heterogenious, you may not be able to manipulate that independently.

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I don't want to let people slide off the hook, because I think we have an important question which, to me, still seems, even though I am not making an official declaration, somewhat arbitrary.

You said that even if we could document that we don't have a pseudospecific effect -- that is one that happens to be a drug working in a demented patient -- that we couldn't say that is a drug for dementia if, in fact, the effect of the drug depended upon the patient being demented.

Remember a diagnosis of an illness may depend on its cardinal signs. But a phenomena of the illness, unrelated to the cardinal sign, could still be important; outbursts, wandering at night, hostile and aggressive behavior. If you had something that altered that, but only in the presence of dementia, not in everyone else, wouldn't that be a legitimate claim?

DR. GAMZU: But you are suggesting that the same drug is tested in all other patients with a wide variety of disease states and found to be not effective.

DR. LEBER: That is a logical maneuver to exclude pseudospecificity. I am just asking the general question.

DR. GAMZU: But isn't that one of your basic assumptions?

DR. LEBER: I want to know where this panel, as august as it may be, would have the right to exclude a

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particular type of claim of that sort. It is a matter of opinion, isn't it?

DR. DRACHMAN: We are into a serious semantic argument here, I think.

DR. LEBER: Not at all. It is a substantive argument.

DR. DRACHMAN: Substantive, but semantic at its root because, in fact, Alzheimer in his first paper described a patient who had severe behavioral disorders and because we are talking about the treatment of Alzheimer's disease rather than just dementia, I do regard behavioral problems, which I like to encapsulate as obstreperous behaviors, as one of the most serious problems of Alzheimer's disease.

Barry alluded to that before. It is, certainly, the most common reason why patients go to institutionalized settings such as nursing homes. The whole issue that you raise about pseudospecificity gives me a certain amount of problem here. Could one, indeed, alter the behavioral disorders in a fairly benign fashion, there are many patients with Alzheimer's disease who would stay in their homes for an extra six months, a year or several years, as a matter of fact.

So even though, in its purest sense, the conceptual notion of dementia really refers to cognitive and memory decline, it its practical sense, behavioral changes occur in

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our studies in about 85 percent of all patients.

DR. WURTMAN: I agree. I think, Paul, the way you phrased the question initially, as I understood it, was whether or not a treatment directed toward another symptom or another transmitter would, by the way, also enhance cognition.

That is not necessarily the case. I think David is quite right. One could treat the obstreperous behavior productively, whether or not by doing so cognition also improves.

DR. LEBER: Let me explain -- this is really a point of reference, because not everyone here may understand what we mean by pseudospecificity. Assume for the moment that I could stop obstreperous behavior by using general anesthesia. It works in everyone, regardless of whether or not they have dementia.

You could not make a claim that that is a treatment of dementia. It is a general effect of the drug. If, in fact, depression, anxiety and all the other ennuis of modern life and distresses were present in early dementia, treating them effectively with drugs that work for those conditions would not fairly be entitled to a claim.

This is a question of equity. That doesn't mean you couldn't use them. It is a question of whether you want to make the claim.

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What I wanted to get away from is the idea, and I think most people would agree, that the real, unqualified antidementia drug probably follows, for most of you, what Dr. Thal has suggested; that is, an effect on the cardinal signs, if you will, of the illness, affecting memory-cognition. That doesn't mean there couldn't be other claims linked to dementia if you could document them.

That is really what I want to get your consensus about.

DR. FERRIS: There are a couple of sides to this. I think I would also like, maybe, to turn the pseudospecificity issue upside-down in the second part of my comments. I would suggest that, as long as there is a consensus on groupings of important symptoms in the clinical syndrome that we call Alzheimer's disease, any compound that can be shown to be efficacious on that cluster of symptoms, if properly defined, could be considered to be an antidementia drug.

But, again, apples and oranges and pears have to be kept separate both in terms of the need to independently assess in an unconfounded way Cluster of Symptoms A, such as behavioral problems versus Cluster of Symptoms B, memory, praxis, language, et cetera.

In other words, we have to be very careful in the design of the study how we assess whether there is an effect on one set of symptoms versus another.

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Related to that comes the issue of what is the claim; in other words, there could certainly be a claim for an antidementia drug where the claim is specific to one group of symptoms such as aberrant behaviors.

DR. LEBER: Let me explain the regulatory problem and the reason we are into this. Let's assume that Dr. Raskin's study had not turned out as it did. Let's assume he was lucky in his sampling and had come up -- and that is a possible explanation for the finding of no difference that he observed -- not that the drug didn't work in that patient population but rather he didn't have the power to detect the effect that does work sometimes, and he had gotten a positive result with a classic drug, Imipramine or Amitriptyline.

Would that allow the makers of those drugs to make a claim they have a drug for depression in dementia? Probably, we would say that they are already known to be antidepressants, and no.

But let's assume it was an undeveloped, not particularly profitable, antidepressant that is languishing on somebody's shelf. And they say, "This is a nice way to get the drug onto the market. We have been unable to develop it commercially. There is no real window opportunity here for this. Let's bring it along for this selected pseudospecific use."

I think that was sort of the thing that got us into

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it, the inequity of, by doing an incomplete workup of a drug, gaining a claim linked, through choice of the investigation, to antidementia.

DR. FERRIS: The other side of this question, though, could be applied to the cognitive symptoms. Let's suppose there were a drug that was effective in a very general way on enhancing the primary biologic substrate that underlies memory functioning and that would imply that this could well be a drug that would enhance memory in any subject population for which there was some relative intactness of that biological substrate.

So it would work in us, and it would work in medical students, it would work in normal old people and it would work, perhaps, at least in the milder end of the dementia spectrum.

DR. LEBER: It would be a great drug.

DR. FERRIS: It would be a great drug and, of course, it has no toxicity whatsoever.

DR. LEBER: What would you call it?

DR. FERRIS: The point is, if you developed that drug specifically for Alzheimer's disease, one could argue that that was an example of pseudospecificity. But everyone will accept that kind of pseudospecificity.

DR. LEBER: It is, but if you wanted to be truthful about that drug, you would say that drug is a cognitive or

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memory enhancer, and it is not predicted on the basis on the basis of one being demented

And that is a fairer and more accurate explanation.

DR. FERRIS: I would apply the same reasoning to an antidepressant that had a broad spectrum of application.

DR. DRACHMAN: Is aspirin pseudospecific for headache? Is that what you are saying?

DR. LEBER: My own judgment on controlled trials on tension headache, possibly. But I haven't reviewed them in great depth, personally, and it's a different kind of pseudospecificity.

DR. DRACHMAN: Or could aspirin be labeled as being useful for headache?

DR. LEBER: Obviously, there is the possibility that drugs are promiscuous in the sense that they have many effects. If you could prove that a drug had a specific effect -- look, this is not something that anybody ordained in the Federal Food, Drug and Cosmetic Act. It is an attempt on what we call local policy to take a fair and reasonable stand on issues that are vexing in drug development.

I am interested in what the panel thinks. I hear a vote for if somebody takes a new product not already marketed and works with it in the demented population and fails to show an effect on the cognitive and memory aspects of

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dementia, but does show an effect on some important sign in dementia, behavior, that we would be willing as a group -- and that is real question -- to accept it as a legitimate antidementia agent.

Is that true?

DR. RASKIN: I sat in on the review of Hydergine, you may recall. The indications for Hydergine came right off the SCAG, the SCAG items. I think there were five SCAG items that showed significant drug-placebo differences. These are exactly the behaviors described on the indication, on the package insert.

DR. LEBER: It is not approved for dementia, though.

DR. RASKIN: That is the point I am making. I think we may be getting into a semantic quibble here. I don't like labels like antidementia drug, antidepressant drug, because they have broad spectra.

Antidepressant drugs treat anxiety and hostility.

DR. WURTMAN: Dementia is a symptom of Alzheimer's disease. What you are saying is the disease has other symptoms. The labeling might be better of this putative drug for the treatment of patients with Alzheimer's who had that symptom as opposed to labeling it as an antidementia drug. Is that a possibility?

DR. LEBER: There are a lot of possibilities. I would be interested in what the panel thinks. Rich Mohs had

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his hand up and he is in the central position which means he is underrepresented.

DR. MOHS: What I think is that if you have a troublesome symptom that people want to have treated, and somebody comes up with a drug that actually helps make that patient better, there ought to be some way to get that approved, assuming that it doesn't have awful side effects.

In the case of a drug, this hypothetical drug which I don't think would ever exist, but let's say that it did, that actually helped in controlling agitation, obstreperousness, but did not improve cognitive function in patients who had Alzheimer's disease, I think that there ought to be a way to get the drug into the people who need it, but I wouldn't want to call it an antidementia drug because dementia -- just to get back to the semantics of it -- dementia, by definition, is a loss of cognitive function.

That is not what you are treating with that drug. You are doing something useful, which I think ought to be allowed and be approved, if it were possible, but I wouldn't want to call it an antidementia drug.

DR. THAL: Would you call it an anti-Alzheimer drug?

DR. MOHS: No. It doesn't stop Alzheimer's.

DR. THAL: Would you call it an anti-obstreperous drug?

DR. MOHS: I would call it Streperase. That's

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what I would call it.

DR. GAMZU: To be given to disputative panels in front of the FDA.

I think I agree with what has been said before that there is a major problem. Nobody denies the fact that behavioral disorders are very important in this group of people. By the same token, incontinence is, as well. If you had a drug for incontinence, it would do very well.

I think if the drug is shown to be effective in the population, it should be approved if it has clinical significance. What you call it is a matter of what is going to go in the labeling, and that is going to be a matter -- it is a totally independent thing. It is the semantics we are talking about.

I don't think that is the question. I think the question is yes, it should be approvable.

One of the things, however, when we started this round of discussion was you suggested a drug for treating, say, depression or agitation in Alzheimer patients. I think that from a sponsor's perspective, and I will speak personally, if I were asked the question, "Should we devote a lot of time and effort to looking for such a drug?" then I think the answer would be no because there would be this danger of specificity.

On the other hand, if we have reason to believe, for

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whatever premises they are, that the drug that we are testing in Alzheimer's ought to be tested in Alzheimer's, and that is one of the outcomes, and it is specified a priori, obviously, before a Phase III trial, then I think even by the rules that you have talked about, that that has to be an approvable drug.

DR. LEBER: I was really asking a much broader question and that is, what does this panel -- this is an external validity issue -- what is it that you are going to allow us to make an assertion that a drug is an antidementia drug. I was just drawing out something which seemed to me to be inherently controlling; that is to say, you can't have it unless you do exactly what I think it should do.

I want to know if everyone agrees. Maybe that is the state of the art. Do you have to have effects on the cardinal symptoms, and I will call them cognition and memory, reason, or whatever you want, to call a drug an antidementia drug?

DR. DAVIS: I think Richard's position is precisely the correct one. It is a drug that has an appropriate indication but is not an antidementia drug. The larger issue that it then raises is what other similar conditions may it be effective in?

The sponsor, I think, should, in fact, determine that, what other conditions it may work in. But if, in fact, we have an agent that is effective for what is a non-

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cognitive, but nonetheless, critical problem in dementia, we should find a way to get that to people.

I think that, though in jest, Elkan talked about urinary incontinence --

DR. GAMZU: Not in jest.

DR. DAVIS: It is an important issue just as is contractures. If someone came out with a drug for contractures in Alzheimer's, I would be surprised if it didn't work in other conditions, but I would be very pleased to have that in the therapeutic armamentarium.

DR. LEBER: Again, it is the side of the issue. It is not so much that we are not interested in approving drugs that have legitimate uses. I am really trying to core in, if you will, on the issue of what this panel would consider to be a legitimate antidementia claim. What is it going to be based on?

I seem to be hearing almost agreement that that name requires cognitive effects on valid outcome measures that look at the content of what we have yet to discuss; that is, what are the content of performances that we are going to consider.

Now, we will probably consider that in the specific session that we have on it, but I am interested in a global way. What kinds of changes do you want for this antidementia effect? This is unqualified.

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DR. DRACHMAN: Elkan said something that I am very, very concerned about. He said that should a drug be under consideration for treatment of obstreperous behaviors, that probably because it isn't specific for dementia, that probably it wouldn't be pursued. I hope I am saying that correctly. Maybe I missed that.

DR. GAMZU: No, no. I said if it were being considered for the treatment of obstreperous behavior in Alzheimer patients I don't think that that is a target that most companies would focus on. If you have a drug that is likely to be useful in obstreperous behaviors, you would be more interested in looking at it in a much broader situation that is probably going to be an antipsychotic.

We tend to focus on the more global issues of what are the unmet medical needs. This is, clearly, an unmet medical need. On the other hand, there are a number of drugs that are actually being used right now and have labeling that suggests, for behavioral manifestations of psychotic disturbances, I believe is the labeling, for quite a few of the antipsychotic agents.

So there are things out there. If the people who are coming to this particular audience -- I am not saying you shouldn't do it, but the people whose focus is in Alzheimer's disease is on the primary factors. You can look at it from a pragmatic perspective.

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Yesterday, some of us were at a presentation where the Wilkerson Group gave their estimate of what the unmet need was. Now, their estimate was couched in dollar figures, but it doesn't really matter. Basically, they said that 10 to 20 percent of the patients would benefit from a drug that would treat these behavioral disorders.

Obviously, for a company making a major decision, the 80 percent of all the other patients and their cognitive loss in that extra 20 percent is a far greater focus. That doesn't mean to say it is not a legitimate avenue.

But most of us, I believe, are not in the business for purely altruistic purposes.

DR. LEBER: Can I cut this discussion off for a reason. I think we are drifting into an issue of almost directional advice on investment possibilities in drug development. That is really not the thrust. The thrust of this is to talk about external validity.

So we have examined what the nature of the claim most people would prefer. I still think it is on this theme of an effect on the cognitive symptoms of dementia. What is it that will make a claim a reasonable one? The next question was the sampling of the patient population. Who should you work with?

We started to get into that. Do you want to use a narrow population because you have some believe that you are

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more likely to demonstate an effect because of ceiling or floor effects which may or may not exist? Do you have some predictive device, or do you want to take unwashed Alzheimer's patients that are acceptably diagnosed?

Let me get to that stage of the discussion.

DR. DAVIS: I think Leon said this very well in his presentation. You would like to take everybody, but there are certain constraints that make it very difficult to take everybody. The instruments don't work in everybody. But if we go beyond the instruments, we have talked about biological heterogeneity. The issue in biological heterogeneity is not so much whether there are different etiologies, though I think there probably are.

The issue is whether there is pharmacological heterogeneity. I think we already know there is pharmacological heterogeneity in this disease. We shouldn't discount all that has gone before the THA study. There are reasons for biological heterogeneity. At the very least, we know there is an inverted U-shaped curve for cholinomimetic agents, but the inverted U-shaped is well-demonstrated in animals.

It is almost a physiological law that you can't infinitely improve things. You can't do it in the heart. You can't do it in muscles. It is not surprising that there would be an inverted U-shaped curve.

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There is also the additional problem in elderly people that 80-year-olds don't have pharmacokinetics like 20-year-olds which also makes it very difficult to find a dose. So when you think about those issues and then add to it, I think, the fact that at autopsy, neurochemically, all these brains are not alike and in therapies, at least as we presently conceptualize them which, at least at this state of the art, is replacement oriented and neurotransmitter driven, and given that there is a heterogeneity of neurotransmitter abnormalities and that there is a growing literature to suggest that the plethora of neurotransmitted abnormalities affect the efficacy of the cholinergic agent, it is quite reasonable to say, beforehand, that not everyone will respond.

We need to develop a strategy that identifies those who may.

What could be addressed about the THA study is, perhaps, as it evolved, it was less than ideal to do that, which may very well be the case. But I don't think we can fall away from the argument that it is, I think, at this point, certainly without substantially more preclinical and then early Phase II data, premature to run a drug in everybody and in all comers.

DR. WHITEHOUSE: Let me just link to that very specifically by making a specific suggestion and claim. There are predictors about the effect of cholinomymetics

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based on the brain changes, based on two statements. Older patients, in several studies, less cholinergic abnormalities and also tend to have less pathology in other systems.

So that would predict, or allow the prediction, that older people might respond better to THA than younger people. If you believe that that is a subtype that is identified on the basis of age, then look at that and maybe stratify that.

DR. DAVIS: Let me readdress that because I think this is a very, very critical question about how these studies are conducted and will be in the future. The older patients are generally patients with multisystem disease. They are patients who, for the most part, are not getting into the study.

So if you look at the average age of the study and compare that, perhaps, to where do we see the greatest prevalence of Alzheimer's disease, we are inevitably shifting toward younger people.

We and lots of other groups, I think, have data that suggest that when you have the disease, as you suggested, at an earlier age of onset, the abnormalities are more severe and the number of systems that are brought into play are more severe.

But I would not be at all surprised that when we come back and look at the THA data, and I am just guessing

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now, but I wouldn't be surprised that, because of the selection biases that happened or the necessity of getting a healthy elderly population, that it will be impossible to see what we all think should be seen based on the autopsy studies.

DR. LEBER: I want to raise important use of terms. One is prediction in the sense of statistical prediction, having a maneuver which reliably allows you to say what fraction -- it is sort of like a conditional probability,the probability of success given this result, like a lab test -- as distinct from what I would call plausible intellectual prediction which says, "Given the theories now extant and the information we have, we believe it would be a good idea."

Now, I don't doubt, Ken, that you are absolutely right, there is loads of data to support and inverted-U-shaped dose-response curve in certain models. But that does not, as you have just suggested, mean that that will actually be documentable or, in fact, useful in designing clinical trials.

It so happens that the particular 971 study that is being done may, in fact, not answer all the question but it will be very interesting to see whether or not patients in particular sequences with particular results, whether those results predict the outcome in the double-blind phase.

I think that kind of thing may give you a lead.

But the whole point I want to distinguish -- theory

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does not necessarily always turn into what is a predictable outcome in clinical trials. That is one of the things that we are talking about, clinical trials.

DR. WURTMAN: To get back to some data that Leon showed that, I must say, I found very depressing. There is rather more heterogeneity among patients in the rate of progression of the disease than one would have thought. It changes from one point to 20 points, or one point to 12 points in the space of one year?

Also, the fact that patients who do very badly in one year don't necessarily do badly in succeeding years. I think that these facts, of necessity, make clinical trials far more difficult than one would have guessed because of the heterogeneity. I would encourage Leon to go home and do 500 more patients so we can see if it is really true.

One of the things Leon said was that there was no relationship between the starting age of the patient and the average rate of progression. This would seem to go against what we have just been discussing. I believed, before walking into this room, that older patients had milder disease, in general.

So I think that is critically important that more data be obtained on this subject. I don't know how long it will take to do that.

DR. LEBER: Another question: is it data? Is it

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source of variance? Are those tests-retests on these patients stable? Could it be day effects, month effects? Concomitant disease effect?

DR. THAL: We actually have test-retest reliability on a lot of the patients. When there is test-retest administration within a short period of time, meaning repeated tests after one, two, three and six weeks, the test-retest reliability in a given patients is quite high and it runs about .85 for all of these tests.

DR. LEBER: So that is not the cause. It really is a heterogeneous disease.

DR. FERRIS: In regard to your central question which is what patients or subgroups of patients would be optimal for selection -- and a lot of people have addressed various constraints -- but I think a very important one relates to the best group for the measures that we have available that are most sensitive for monitoring the symptoms we are interested in.

And this, in part, I think, is what has been behind the general assumption, which I still think is a good one, that we really ought to look at the relatively mildly impaired patients provided that they meet the specific criteria for Alzheimer's disease, in terms of their severity, which gets into another set of issues in terms of what about patients who are even a little too mild in trials.

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Nevertheless, provided we accept Leon's suggestion that we, at least, must take patients with probably Alzheimer's disease, and that relates in part to how severe the symptoms have to be, I would suggest that the measures we now have available, whether it be even the global measures, but, in particular, the objective cognitive assessments, have the greatest utility and the greatest sensitivity for measuring the treatment effects.

So we really ought to stick with the milder group where those measures can be used. One could also argue in biological terms, in terms of the amount of pathology that presumably is present in the milder patients, more opportunity for a pharmacologic intervention to something, and so forth.

These are all the underlying assumptions.

Getting back to this milder group, since I would suggest that there are three primary kinds of outcome measures, and there are sessions here to address each of them, the objective cognitive test, Leon talked about two of them, the more global comprehensive measures such as the Mini-Mental State and the ADAS, et cetera, and also the Activity of Daily Living Scales, the third would be the Objective Cognitive Test.

One assumption that I would make, at least in ordinal terms, is that those three domains of measurement differ with respect to sensitivity or ability to detect

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fairly small changes. I think the least sensitive would be, probably, the Activity of Daily Living Scales. Somewhere in between would be the comprehensive or global measures. I believe the most sensitive to pick up small effects, perhaps in a very selected cognitive area, would be the psychometric or objective measures.

I would suggest that, at least during the course of early drug development, all three are essential because you wouldn't want to miss something by leaving out the more sensitive objective cognitive tests.

DR. LEBER: You are also arguing, though, that part of our sampling for patients is going to be driven by the sensitivity of the instruments that are available so that we would not want to go into an area, even though that is where the truth lies, because we don't have the instrumentation for it, in part.

So you are going to be selectively picking people who are less impaired because you can examine a broader range of pathologies. Interesting. Do people agree with that?

DR. GAMZU: No. I strongly disagree with that. I think if you are asking about subpopulations -- Steve said something earlier that we just don't have any information on the subpopulations, and Paul emphasized that again. We have all sorts of theories, some of which may be correct and some of which may not.

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It is also interesting that people used to think that cerebral vasodilators would solve the problems of hardening of the arteries and that was wrong, too, but it was seriously believed at the time.

I really think that until we have an effective agent that will allow us to parse out and give us real data to answer some of these questions that we ought to be looking at as broad a population as possible and using broad clinical measures, not the specific measures.

I certainly think that that gives you a better opportunity of finding something that might be there. There might be subpopulations. There may be inverted U-shaped functions. Despite all the work in animals, except for the fact that in patients studied with physostigmine have a single-point dose, an inverted V which may or may not be real, there is no evidence yet in humans that that really does exist.

I do not think that it is the case that you would find that with all drugs. I think the rate-limiting factor for most drugs is toxicity and not the so-called benign inversion of the U-shaped function.

Even if we take the assumption that an enriched population will help us solve some of these problems, again, I do not believe that there is sufficient evidence to say that that design is necessarily the best design.

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There is work from the Columbia group that suggests that that patients that did not respond in the titration phase may respond subsequently. We have heard talk today about how long do you have to treat. The titration phase in the tacrine study, which is the generic name for THA, that stage, at the moment, is two weeks.

But I don't think anybody here would agree that the minimum time to treat patients to show efficacy is two weeks. I can tell you that, from our own experience in this and many other studies that over a two-week period at the beginning of a study, patients on placebo will improve.

But we also know from the longitudinal studies that if you go long enough, they will decline. So you are taking a short period, you are making a brief putative assessment of response, and making the assumption that that is going to be replicated in a longer period of time.

Is the enriched-population design important? I think until we have some results, we won't know. We certainly will not know from this study the answer to the question that Steve posed, and this is does it drop patients who might otherwise have responded?

So I would say cast the net as broadly as possible. I think the enriched-population design for the tacrine study was crucial, but not because of theoretical aspects that we are talking about now, but a lot more to do with safety

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aspects.

DR. LEBER: We are running out of time, but you brought up, Elkan, a very important issue that relates to time. Given what we have all been discussing so far, is there a minimum duration for any kind of clinical trial that you would demand before you would be willing to accept the results as reasonably a source of information to make a claim as an antidementia drug.

Anybody want to deal with that? Minimum time, now. Weeks? Months? Half a year? Five days? Any thoughts?

DR. RASKIN: Let me go back to an earlier -- it sort of ties into what you are asking and to what has been said. I don't think there is any question, and certainly it was demonstrated in the hypobaric oxygen study, that there is a placebo effect if you take in mildly-demented patients. So to that extent, I think, first of all, you have to have something that will measure that. I will talk about that maybe a little bit tomorrow.

But, beyond that, you should run the study long enough so that there is a chance for that to wash out.

I was just having a little discussion with Gil about what that is. We used to study placebo effect, it was sort of a major area of concern, very early on, with some of the drug trials. It hasn't been lately, but I don't know

what the placebo effect is in this population.

In others, it has been much shorter.

DR. THAL: I think Ken or I could answer that. In reality, if you use objective instruments, we see essentially no placebo effect. If you look at what the family tells you, you see a placebo effect.

DR. RASKIN: I will show a slide tomorrow that demonstrates a placebo effect in early Alzheimer's with an adjective chest list.

DR. THAL: Not with a measure of cognitive ability such as a list-learning task

DR. CROOK: No, but I think you can show that, too. Like many of these issues, it comes back to severity. In the less-severely impaired patients, you clearly do see an effect on objective measures.

The same with Elkan's point; in these less-severely impaired patients, cognition is a complex phenomenon as it is in humans. It is multifactorial. Drugs may have effect on some parameters of cognitions, and not others. I think it is worth looking in much greater detail with objective test in those patients.

By the time the disease has progressed so that it is essentially a unitary phenomenon, many of the functions have been compromised and a global assessment might be enough. But I think severity is an issue that overrides many

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of these considerations.

DR. DAVIS: You started, in your keynote comments, and pointed out how many things we don't know. This isn't like developing antidepressants. We took our best shot at a reasonable protocol with THA and would probably do it differently today because we have learned.

The number of things we don't know, including how long to treat, is an example of just one. On that issue, Marshal Folstein has some terrific data from head studies that were acute with physostigmine, seeing differences on a praxis task and on a PET study.

When Rich and I did our IV physo, it was very acute. Yet, now, we noting things that suggest that you can see effects that are much longer. The implications of that are what Elkan said; the dose-finding phase, then, may miss some people.

All unanswered questions. The only way we are going to answer them is if we take the time in other studies to variate from the standard design.

DR. DRACHMAN: I think that is a theme that I hear occurring throughout this morning, at least; that is, the number of permutations and combinations of patients, degrees of severity, types of trials, types of measures, et cetera, is so great that the idea of zeroing in with a single type of trial -- that is, two weeks, patients with a specific degree

of deficit, pure AD, only on the memory, et cetera, that idea is probably rather destructive instead of being creative.

I think at this point, we aren't ready to do that. I hope that that is what you are hearing. I think that is what I hear from the panel, that we aren't ready to do that and that even though there is a clear message about the importance of doing that at some point, before the regulatory process accepts the drug as being effective and safe in a defined population, I think that what we have to do is spread a net, just exactly as Elkan said.

DR. LEBER: I think that is a very eloquent statement to end this session. I want to thank you all. I think in a way, Dave, that you are echoing the earliest things I said about why we don't have guidelines. The world is a little too complex for us to have closure on it.

I thank you all for illustrating that so clearly.

[Proceedings were recessed for lunch from 12:30 p.m. to 1:15 p.m.]

EXHIBIT 42

Nivalin and its Curative Effect upon Diseases of the Nervous System

by K. G. Pernov

I. Pharmacodynamics

The theory on the chemical transmission of nerve impulses was developed during the first three decades of the 20th century from the work of a number of researchers (Langlay, Elliot, Mislawski – 1905, Dale – 1914 and Loewi – 1921). This theory [illegible] exciting avenues for therapeutic application. Researchers eagerly endeavored to boost chemical neuro-transmitter action, etc., either by directly introducing them into the organism or by using substances to block the antagonists to transmitter activity.

Many preparations were considered in this regard. Among them, two groups of substances having a cholinesterase-inhibiting effect are especially significant.

The first group comprises substances which reversibly inactivate the cholinesterase (represented by eserine). The second group consists of phosphororganic substances which produce an irreversible inactivating of the cholinesterase. Diisopropylfluorophosphate (DFP) is indicative of this group.

A new, more powerful cholinesterase inhibitor having a reversible effect is the Bulgarian preparation Nivalin (Galantamine hydrobromide), isolated (I. Iwanowa-Boubewa – 1957) from the snowdrop plant growing wild in Bulgaria (Galanthus nivalis, var.: gracilis, family: Amarillidaceae). Its chemical composition is that of an alkaloid of the phenanthridine group having a tertiary nitrogen atom. D. Paskov suggested its base pharmacological properties (1959). Nivalin is a preparation which, while similar to eserine and prostigmin, exhibits its own specific characteristics. Experimental tests conducted by D. Paskov determined that it reversibly blocked cholinesterase at both the M-cholinreactive systems of the effector organs as well as the N-cholinreactive systems of the vegetative ganglia. This phenomenon was confirmed by more recent bio-chemical studies (G. Chistoni, G. Guarraldi) and electromyographic observations (V. Bergamini, P. Baggiore), as well as by clinical experiences made with late recovery from myasthenia gravis pseudoparalytica and that occurring some months following treatment with Nivalin. Nivalin intensifies the acetylcholine action in the central nervous system and in the smooth and striated musculature; it also activates acetylcholine's hypotensive effect. Contractures of the striated musculature are not only intensified by the acetylcholine accumulation but also by the direct effect of the Nivalin on the cholinreactive systems. It stimulates respiration, and its pronounced anticurare action arises from the mechanism of competitive effect in the neuromuscular synapse region. Nivalin facilitates the conduction of impulses in the nervous system and thereby increases reflex excitability, shortens the latency of the reflexes and boosts the process of excitation in the cerebral cortex.

Recent studies by M. D. Maschkowski and R. J. Iljutschenok on the bioelectric activity in the brains of cats and rabbits showed that Nivalin's mode of action is similar to that of eserine, although it differs substantially from prostigmin. At medium doses, Nivalin causes rapid-onset changes to the basic electroencephalogram rhythm, similar to the "arousal reaction," while prostigmin induces similar changes only at lethal doses and only after 50-60 minutes.

This difference in effect firstly between Nivalin and eserine and secondly with respect to prostigmin is to be explained by the fact that Nivalin and eserine are tertiary amines while prostigmin is a quaternary amine. As is generally known, of course, quaternary amines enter the central nervous system much more slowly and have a substantially weaker effect than the tertiaries.

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